REMARKS

Entry of the foregoing, reexamination and reconsideration of the subject application, as amended, are respectfully requested in light of the following remarks.

Status

Prior to the instant Response, and as is correctly reflected in the Office Action Summary mailed November 5, 2010, Claims 1-18 were pending. *Office Action mailed November 5, 2010, Office Action Summary, Item 4*. Claims 7-9, and 13 were withdrawn. *Id. at Item 4a*. Claims 1-6, 10-12, and 14-17 stand rejected. *Id. at Item 6*.

By the present amendment, Claim 1 has been amended to recite that the hydrophilic macromolecule is introduced as a phospholipid derivative of the hydrophilic macromolecule. Support for the amendment can be found in original claim 13, which has been canceled.

It is recognized that claim 13 was withdrawn from consideration because the Examiner considered that claim 13 did not read upon the election of PEG as the hydrophobic macromolecule. However, it should be understood that the subject matter of claim 13 that has now been incorporated into claim 1 relates to the manner in which the hydrophobic macromolecule (*e.g.* the elected PEG) is introduced (*i.e.* how the PEG is attached to the outer surface of the vesicle). The manner in which the hydrophobic macromolecule is introduced to the vesicle was not subject to a requirement for election. Thus the claim as amended is believed to continue to read on the species elected for examination.

The claims have been further amended in matters of form to better describe the claimed invention.

These amendments are made without prejudice or disclaimer of any subject matter. Applicants reserve the right to file a continuation or divisional application directed to any subject matter that may have been canceled by these amendments.

Rejections Under 35 U.S.C. § 103(a) - Harigai and Mayer

Claims 1-6, 10-12, and 14-17 stand rejected under 35 U.S.C. § 103(a) as allegedly anticipated by Harigai et al., "Preferential Binding of Polyethylene Glycol-Coated Liposomes Containing a Novel Cationic Lipid, TRX-20, to Human Subendothelial Cells via Chondroitin Sulfate,"18(9) Pharmaceutical Research 1284-1290 (September 2001) ("Harigai") in view of U.S. Patent No. 5,616,341 to Mayer et al. ("Mayer"). *Office Action mailed November 5, 2010, Pages 2-7.* The rejection is are respectfully traversed.

The rejection lacks the legally-required factual basis for the combination of references to arrive at the claimed invention. The rejection contends that it would be obvious for a person skilled in the art to combine the disclosures of Harigai and Mayer and incorporate phosphatidylcholine into a liposome modified with PEG on its exterior surface for the delivery of anticancer drugs. The rejection contends that one of ordinary skill in the art would purportedly have a reason to make the proposed combination under the rationale of "combining prior art elements according to known methods to yield predictable results." M.P.E.P. § 2143(A).

To reject a claim based on this rationale, Office personnel must resolve the Graham factual inquiries and then articulate the following:

> (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;
> (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;
> (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and
> (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. *Id.*

In this case, the Applicants submit that the record lacks support for the elements necessary to make out a prima facie case.

The Examiner has acknowledged that Harigai is a study of binding ability between liposomes and cells. Harigai prepares liposomes containing a rhodamine label incorporated into the liposomal membrane. Applicants have pointed out that Harigai does not teach preparing liposomes containing drugs in the closed interior space of the liposome, let alone drugs which are unstable at low pH. Any implication by Harigai as to their liposomes' effectiveness as drug delivery vehicles is purely speculative. More importantly, Harigai never addresses the pH of the interior aqueous phase. However, it is clear that the liposomes of Harigai contained an environment of physiological saline which is at neutral pH. Harigai does not suggest that their liposomes could effectively contain an acidic environment or address the issue of interior pH. Thus, Harigai does not contemplate or suggest a solution to the problem addressed by the present invention.

The present inventors sought to solve the problem of stability when a liposome preparation must contain a drug that is stable only at acidic pH and is unstable at neutral pH. The problem presents a conundrum because, in the past, if the interior phase of the liposome preparation was maintained at neutral pH, certain drugs which are unstable at neutral pH could not be stably maintained in liposomes. On the other hand, if the interior phase of the liposome were maintained at low pH, the liposomes were unstable. By the present amendment, Claim 1 has been amended to recite that the drug in the claimed preparation is a drug for which such a solution would be desired.

To solve this problem—which is not addressed in the prior art—the present inventors made the unpredictable discovery that a stable liposome preparation could be made with unilamellar vesicles having an interior aqueous phase at a pH of up to 5 containing a drug loaded therein and a hydrophilic macromolecule only on the exterior surface of the vesicles..

Mayer fails to remedy the deficiencies of Harigai. Mayer is directed to a process that loads drugs into liposomes using a transmembrane ion gradient, preferably a transmembrane pH gradient. Mayer's pH gradient is not directed towards ensuring the stability of the drug loaded therein. Thus, Mayer is not concerned with solving the problem that has been appreciated and solved by the present inventors.

The Examiner has pointed out that Mayer discloses that their liposomes may contain PEG modified cholesterol derivatives. By the present amendment, Claim 1 has been amended to recite that the hydrophilic macromolecule is introduced as a phospholipid derivative of the hydrophilic macromolecule. Mayer does not teach or

suggest introduction of a PEG-phospholipid derivative. Thus, the cited art does not teach all of the elements of the invention. Furthermore, neither Mayer nor Harigai suggests a reason to both modify Mayer and combine it with Harigai to arrive at the combination and arrangement of elements specified in the present claims.

Mayer's mention of PEG-cholesterol is merely that, a single mention without any explanation that would lead toward the present invention. Mayer does not suggest that PEG be confined to the outer surface. Mayer does not suggest that PEG-cholesterol would have any beneficial effect on the stability of vesicles having a low interior pH. Instead, Mayer proposes lyophilization as a means to enhance long term storage *See, Mayer col. 16-17.* Thus, it is apparent that Mayer did not appreciate the problem solved by the present invention, or suggest the present invention and the solution it provides.

In stark contrast to the deficiencies in the prior art, the present specification demonstrates that confining the hydrophilic macromolecule, e.g. PEG, to the exterior surface of a vesicle having a pH below 5 provides a surprisingly effective solution to the problem of vesicle stability when a liposome preparation must contain a drug that is stable only at acidic pH and is unstable at neutral pH. Indeed, as the data presented in Test Example 2 (paragraph [0088]) and Figure 3 demonstrate, restriction of the PEG to the outer membrane of the liposome preserves the stability of PEG5000-DPSE in low pH containing liposomes. Thus, the liposome of the instant application will have less instabilization of the lipid bilayer, less leakage of the drug introduced in the liposome, less aggregation of the liposome, a prevention of the decrease in the effect of

preventing adsorption of the liposome to plasma protein or opsonin protein, and prevention of the loss of liposome stability in blood and the like.

To make out a proper rejection requires an explicit analysis articulating a reason for combining the particular elements and features recited in the claims. *See KSR Int'l Co. v. Teleflex Inc.*, 550 US 398, 418, 82 U.S.P.Q.2d 1385, 1388 (2007) (*citing In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329 (Fed Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness")).

Even if the teachings of Mayer and Harigai were combinable, the rejection does not provide any articulated reasoning with some rational underpinning to show why one would do so. To confine a hydrophilic macromolecule to the exterior of a vesicle requires a separate extra step after the vesicles have been formed. There is no reason given in the rejection to explain why one would take the extra trouble to limit the hydrophilic macromolecule to the exterior surface of a drug containing liposome preparation. Neither Mayer nor Harigai provided a reason to undertake this extra step. Thus, the most the rejection can muster is to allege that all the elements were known between two references that separately disclosed liposome preparations. *See Office Action dated November 5, 2010, at 6-7.* That is not sufficient. *See KSR Int'l Co. v. Teleflex Inc.*, 550 US 398, 418, 82 U.S.P.Q.2d 1385, 1388 (2007).

Double Patenting

Claims 1-6, 10-12, and 14-17 were rejected on the grounds of non-statutory obviousness-type double patenting over Claims 1-17 of U.S. Patent No. 5,676,971 in view of Harigai and Mayer. Office Action mailed November 5, 2010, Pages 8-9. These rejections are respectfully traversed.

Applicants submit that the claims in the instant application are patentably distinct from the invention claimed in U.S. Patent No. 5,676,971. Neither Harigai nor Mayer provides a sound scientific reason to modify the invention claimed therein to arrive at the present invention.. The present invention solves a problem that was not suggested by the claims of U.S. Patent No. 5,676,971, Harigai or Mayer. Thus, the present invention is not obvious in view of the patented invention and is separately patentable.

CONCLUSION

In the event that there are any questions relating to this Amendment And Reply, or to the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 836-6620 so that prosecution of the application may be expedited. The Patent Office is hereby authorized to charge any necessary fees, or credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

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